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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/120,030	07/21/98	GOLDSTEIN B	1102870-0456

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HM12/0604

EXAMINER	
BORIN, M	
ART UNIT	PAPER NUMBER
1631	13

DATE MAILED: 06/04/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/120,030	Goldstein et al.
Examiner	**Art Unit**
Michael Borin	1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 19, 2001*

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *4, 5, 28, 29, and 32-55* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideratio

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *4, 5, 28, 29, and 32-55* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. The request filed on 3/19/2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/120030 is acceptable and a CPA has been established. An action on the CPA follows.

For clarity, each of the outstanding rejections in this case are restated below and is followed by response to arguments presented by applicant in responses to both non-final and final Office actions in the parent case.

Status of Claims

2. Claims 4,5, 28,29,32-55 are pending.

3. Claims 4, 5, 28, 29 are rejected are rejected under 35 U.S.C. 103(a) as obvious over Zygmunt or Stark or Goldberg and further in view of Oldham. The rejection is maintained for the reasons of record:

The instant claims are drawn to method of treating staphylococcal infection comprising administering effective amount of at least one recombinantly produced lysostaphin analog and to the pharmaceutical composition comprising the recombinantly produced lysostaphin analog. A lysostaphin analog is defined as recombinantly produced lysostaphin, its mutant variants or any related enzyme that retains proteolytic activity.

Zygmunt

Zygmunt et al review properties of lysostaphin and its *in vitro* and *in vivo* applications. The reference teaches that lysostaphin is effective against a wide variety of staphylococcal infection, and

is more potent than penicillins. Lysostaphin is effective against strains of S. Aureus which are insensitive to other antimicrobial agents, such as cloxacillin, oxacillin, cephalothin (p. 314), and in particular, strains insensitive to methicillin (p. 314,316,317). Similar to its *in vitro* effect, lysostaphin is effective *in vivo* against a wide variety of staphylococcal infections. The reference describes treatment of staphylococcal infections in various organs, such as kidney, heart valve (pages 319-325). The dosage of lysostaphin varies in the range of 0.5 to 50 mg/kg (p. 320, Table 4). The ways of administration are intravenous, intraperitoneal, topical, intranasal (pages 319-324). Combined therapy with other antimicrobials, such as methicillin, augments effect of lysostaphin (p. 322). The reference also teaches pharmaceutical compositions comprising lysostaphin.

Stark (N.Engl. J. Med, 291, 239-240, 1974; see specification, p. 3, lines 21-25).

Stark et al describe that parenteral systemic administration of lysostaphin reduces bacteremia caused by strain of S. *Aureus* which proved to be resistant to methicillin, vancomycin and cephalothin. Single treatment with 500 mg of lysostaphin rapidly cleared microorganisms from pustule sites. The treatment removed staphylococci from blood, lungs, or abscess site. In particular, the reference teaches pharmaceutical compositions comprising lysostaphin, suitable for systemic or parenteral administration.

Goldberg

Goldberg et al describe use of lysostaphin in treatment of staphylococcal endocarditis in dogs. Lysostaphin was administered intravenously in doses 5-50 mg/kg at intervals 1 to 24 h. Lysostaphin treatment resulted in decreased number of staphylococci in lung, liver, spleen, kidney,

aortic and mitral valves. See abstract. The reference teaches pharmaceutical compositions comprising lysostaphin, in particular suitable for parenteral administration.

The primary references do not teach recombinant lysostaphin or use thereof. It is well established in the art that recombinant way of production of proteins is easier and more effective than non-recombinant methods (such as organic synthesis or purification). Oldham reference is used to demonstrate that lysostaphin can be produced recombinantly and that the product produced thereby has high antimicrobial activity similar to that of the natural product.

Oldham

Oldham et al teaches that lysostaphin can be produced recombinantly and demonstrates that recombinant lysostaphin, at low concentration of 5 µg/ml, is effective against *S. Aureus* in mammary tissue. See abstract.

It would have been obvious to one skilled in the art at the time the invention was made to be motivated to use recombinant lysostaphin instead of the natural lysostaphin used in the primary references, because it is easier to produce a recombinant analog of a natural product and because Oldham demonstrated that recombinant lysostaphin has high antimicrobial activity, similar to the natural product.

Further, in regard to lysostaphin analogs and use thereof, it is well known in the pharmaceutical art to develop and use new, improved analogs of known pharmaceuticals. As mechanism of action of lysostaphin is the lysis of the membrane wall of staphylococci, it would be obvious to develop and use new, more potent analogs of this well known antibiotic. Specification, p. 1, lines 26-34, is cited to exemplify lysostaphin analogs known in the prior art.

In regard to various locations of treatment, as Zygmunt teaches that lysostaphin is effective against more than 300 staphylococcus species and suggests its wide use at various locations, and as Stark suggests use of lysostaphin for treatment of human staphylococcal infections in lung, liver, brain, endocardium, and bone, it would have been obvious to an artisan to apply this versatile antimicrobial at the sites which require antimicrobial treatment with the expectation, in the absence of evidence to the contrary, that such treatment will be successful.

Response to arguments

Applicant traversed the Oldham reference pointing to the differences between the claims and the disclosure in the reference. Applicant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. It has been well established that the test for combining references is not what individual references themselves suggest but what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. *In re McLaughlin,* 170 USPQ 209 (CCPA 1970). In the instant case the reason for citing Oldham reference was to demonstrate that , in addition to the general understanding of advantages of the use of recombinant peptides over their natural analogs, prior art does demonstrate that lysostaphin has been produced recombinantly, and that its high antimicrobial activity are similar to the natural product.

Applicant argues that it would not have been obvious to use recombinant lysostaphin (or its analogs) instead of lysostaphin (or its analogs) produced by non-recombinant methods. Broad spectrum antimicrobial effect of lysostaphin is well established in the art. Further, it is well established in the art that recombinant way of production of proteins is easier and more effective than non-recombinant methods (such as organic synthesis or purification). Oldham reference is used to demonstrate that lysostaphin can be produced recombinantly and that the product produced thereby has high antimicrobial activity similar to that of the natural product.

The argument that Oldham demonstrates activity of recombinant lysostaphin only in mammary tissue is not convincing. While it may not be absolutely certain that recombinant lysostaphin will be as effective in treatment of infections in other locations as in mammary tissue, a *prima facie* case of obviousness does not require absolute predictability of success. See In re O'Farell, 7 USPQ2d 1673 (CAFC 1988). In view of the similarity of effects of recombinant and non-recombinant lysostaphins in mammary tissue, and in view of the known broad range of antimicrobial activity of lysostaphin, effectiveness of recombinant lysostaphin (or its analogs) would have been expected to be similar in other sites of microbial infection as well.

4. Claims 32,35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zygmunt or Stark or Goldberg in view of Oldham as applied to claims 4,5,28,29 above, and further in view of Dixon.

The instant claims are drawn to combination therapy of lysostaphin and another antimicrobial, in particular rifamycin or a glycopeptide. The primary references do not teach combined use of lysostaphin and rifamycin or a glycopeptide. However, Zygmunt teaches that a single dose of lysostaphin is effective against staphylococcal infection only for limited time, and it is preferable to follow lysostaphin with another antibiotic. Dixon et al. teach that it is preferable to use lysostaphin in combination with other antimicrobials because a single dose usage of lysostaphin reduces dangers of hypersensitivity reaction. See p. 63, first paragraph. Because combination therapies for treatment of staphylococcal infection are well-known in the art and because it would have been desirable to use plural therapies in order to maximize the probability that staphylococcal infection is minimized, it would be *prima facie* obvious to one of ordinary skills in the art at the time the invention was made to be motivated to use the lysostaphin not only as a sole active pharmaceutical agent, but also in combination with other commonly used antimicrobials, such as rifamycin or glycopeptides.

Response to arguments

Applicant argues (p. 8) that the combination of references does not teach use of recombinant lysostaphin in combination with rifamycin or a glycopeptide. The obviousness of the use of recombinant lysostaphin as an antimicrobial instead of non-recombinantly produced lysostaphin is discussed in the preceding paragraphs. Because combination therapies for treatment of staphylococcal infection are well-known in the art and because it would have been desirable to use

plural therapies in order to maximize the probability that staphylococcal infection is minimized, it would be *prima facie* obvious to one of ordinary skills in the art at the time the invention was made to be motivated to use the lysostaphin not only as a sole active pharmaceutical agent, but also in combination with other commonly used antimicrobials, such as rifamycin or glycopeptides.

5. Claims 33,34, 36-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zygmunt and Stark and Goldberg and Oldham.

The instant claims are drawn to particular dosage ranges. The primary references teach use of different dosages and different ways of administration of lysostaphin. If there are any differences between dosage ranges as claimed and that of the prior art, the differences would be appear minor in nature. Absent some teaching to the contrary, determination of particular ranges employed is within the skill of the ordinary worker as a part of the process of normal optimization.

Conclusion.

6. No claims are allowed

7. This is a CPA of applicant's earlier Application No. 09/120030. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the

mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (703) 305-4506. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Michael Woodward, can be reached on (703) 308-4028. The fax telephone number for this group is (703) 305-3014.

Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MICHAEL BORIN, PH.D
PRIMARY EXAMINER